Results From a Randomized, Open-Label, Crossover Study Evaluating Pharmacokinetic Interaction Between the Aldosterone Synthase Inhibitor Baxdrostat and Metformin in Healthy Human Subjects

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Abstract

Type 2 diabetes mellitus (T2DM) and hypertension are 2 of the leading causes of cardiovascular disease in the US,[1, 2] and 69% to 82% of patients with T2DM also have hypertension.[3, 4] Metformin is the first-line pharmacologic treatment for T2DM.[5, 6] Baxdrostat (CIN-107) is a selective, small-molecule, aldosterone synthase inhibitor with potential as an anti-hypertensive drug. Baxdrostat and metformin could be prescribed together for patients with T2DM and hypertension. Studies with human liver microsomes suggest that baxdrostat inhibits the activity of both multidrug and toxin extrusion (MATE) and MATE2-K transporters. Metformin is a known substrate of MATE.[7, 8]

The objective of this study was to assess the impact of baxdrostat on the pharmacokinetics (PK) of metformin. Safety and tolerability for coadministration of both drugs were also evaluated.

Introduction

Type 2 diabetes mellitus (T2DM) and hypertension are 2 of the leading causes of cardiovascular disease in the US,[1, 2] and 69% to 82% of patients with T2DM also have hypertension.[3, 4] Metformin is the first-line pharmacologic treatment for T2DM.[5, 6] Baxdrostat (CIN-107) is a selective, small-molecule, aldosterone synthase inhibitor with potential as an anti-hypertensive drug. Baxdrostat and metformin could be prescribed together for patients with T2DM and hypertension. Studies with human liver microsomes suggest that baxdrostat inhibits the activity of both multidrug and toxin extrusion (MATE) and MATE2-K transporters. Metformin is a known substrate of MATE.[7, 8]

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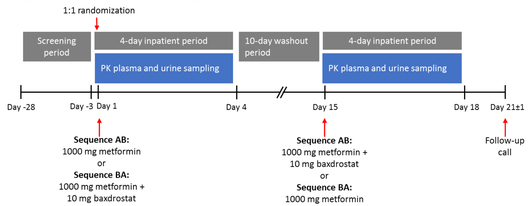
Methods

Healthy volunteers with normal renal function were recruited for the phase 1, randomized, open-label crossover study (**Figure 1**) and given either metformin alone or metformin following a dose of baxdrostat. Blood and urine were collected for PK analyses. Safety was assessed by adverse events, physical examinations, vital signs, electrocardiogram, and clinical laboratory tests.

Figure 1. Study Design



Abbreviation: PK, pharmacokinetic.

Methods (cont'd)

A study size of 24 subjects, including 12 per treatment sequence with an intended correlation value of 0.55, was calculated to provide 80% power to reject the null hypothesis of nonequivalence. An absence of a drug–drug interaction is indicated by 90% confidence intervals of the geometric mean ratio within 80% to 125% for maximum observed plasma concentration (C_{max}) and area under the curve (AUC) PK values.

Results

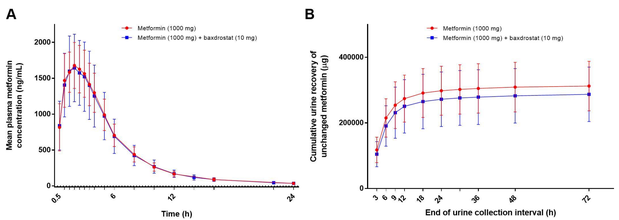
Subjects

Twenty-seven subjects were randomized. Most study participants were male (70%), White (56%), and not Hispanic or Latino. The average age was 37 years and mean body mass index was 25.6 kg/m^2.

PK

Plasma results showed that baxdrostat did not significantly affect the concentration of metformin over time (**Figure 2A**). Cumulative amounts of metformin excreted in the urine were similar in the presence or absence of baxdrostat (**Figure 2B**). The ratio of PK parameters between treatments (metformin and baxdrostat vs metformin alone) was within the range to exclude a drug–drug interaction (**Table 1**).

Figure 2. Plasma (A) and Urine (B) Metformin Concentrations vs Time



A: Data are mean ± standard deviation.
B: Data are least squares mean ± 90% confidence intervals.

Results (cont'd)

Table 1. Summary of PK Parameters for Metformin

PK parameter of metformin	Treatment					
	Metformin alone		Metformin + baxdrostat		(M+B)/M	
	n	GM (CV%)[a]	n	GM (CV%)[a]	n	GM LS ratio (90% CI)[b], %
C_{max} (ng/mL)	26	1732.62 (20.1)	27	1723.37 (30.0)	26	98.84 (91.3, 107.0)
$AUC_{0\text{-}t}$ (h*ng/mL)	26	11024.21 (15.9)	27	10688.87 (26.5)	26	96.77 (90.7, 103.2)
$AUC_{0\text{-}inf}$ (h*ng/mL)	25	11087.78 (15.9)	26	10965.41 (26.3)	24	100.16 (94.4, 106.3)
CLR (L/hr)	26	27.62 (16.8)	27	25.77 (25.9)	NA	NA
$A_{e\ (0\text{-}72)}$ (ug)	26	304520.62 (22.6)	27	275459.85 (30.5)	NA	NA

[a] Geometric CV% = 100(exp(SD^2)-1)$^{0.5}$, where SD is the standard deviation of the log-transformed data.
[b] A 90% CI within the boundary of 80% to 125% is the requirement to claim no effect of baxdrostat on metformin PK parameters.
Abbreviations: $A_{e\ (0\text{-}72)}$, total amount excreted in urine from time 0 to 72 hours after dose; AUC, area under the plasma concentration-time curve; $AUC_{0\text{-}t}$, AUC from time 0 to last quantifiable plasma concentration; $AUC_{0\text{-}inf}$, AUC from time 0 to infinity; B, baxdrostat; CI, confidence interval; CLR, renal clearance; C_{max}, maximum observed plasma concentration;, CV, coefficient of variation; GM, geometric mean; LS, least squares; M, metformin; NA, not available; PK, pharmacokinetic.

Safety

Overall, 7 subjects experienced a total of 15 treatment-emergent adverse events (TEAEs; **Table 2**). No TEAEs resulted in withdrawal or death. No noteworthy increases in incidence or severity of TEAEs were observed when subjects received metformin and baxdrostat compared with when they received metformin alone. No clinically meaningful changes were observed in physical examinations, vital signs, electrocardiogram (including no QT prolongation), or clinical laboratory results.

Table 2. Summary of Adverse Events

Adverse events	Treatment	
	Metformin (n=26)	Metformin + baxdrostat (n=27)
Any TEAE, n(%) e	5 (19.2) 6	6 (22.2) 9
Key TEAEs by MedDRA class, n(%):		
Gastrointestinal disorders	4 (15.4)	5 (18.5)
Diarrhea	3 (11.5)	4 (14.8)
Abdominal pain upper	1 (3.8)	1 (3.7)
Flatulence	0 (0.0)	1 (3.7)
Nausea	1 (3.8)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (7.4)
Dizziness postural	0 (0.0)	1 (3.7)
Presyncope	0 (0.0)	1 (3.7)

TEAEs are defined as any adverse event, regardless of relationship to the study drug, which began after the first dose was administered.
Abbreviations: e, events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Discussion/Summary

Coadministration of baxdrostat did not significantly affect the plasma PK of metformin or cumulative amounts of metformin excreted in the urine. Administration of metformin did not significantly affect the PK parameters of baxdrostat compared with previously published data;[9] thus, study validity was demonstrated.

Safety data from this study suggest that baxdrostat does not increase the risk of adverse events when coadministered with metformin. The most common TEAEs with coadministration of metformin and baxdrostat were gastrointestinal disorders, which are commonly associated with metformin treatment.[10] Because this study was conducted in healthy subjects, further investigation is warranted to confirm the safety and efficacy of baxdrostat in patients with comorbid hypertension and T2DM.

Conclusions

Metformin and baxdrostat were safe and well tolerated when coadministered. Dosage adjustment is unlikely to be required in patients with T2DM and hypertension who are concomitantly receiving metformin and baxdrostat.

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